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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,394	06/02/2005	Francois Romagne	INN-123	8478

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/537,394	ROMAGNE ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-107* is/are pending in the application.

4a) Of the above claim(s) *89,96-99 and 103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-88,90-95 and 100-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's request for continued examination filed on July 2, 2009.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Status of Claims

Amendment of claims 80, 95, 99 and 100; and addition of claims 104-107 is acknowledged.

Claims 80-107 are currently pending and are the subject of this office action.

Claims 89, 96-99 and 103 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions/species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 19, 2008.

Claims 80-88, 90-95 and 100-107 are presently under examination.

The following species are under examination: 3-(bromomethyl)-3-butanol-1-yl-diphosphate (BrHPP or Phosphostim) as the gamma-delta T cell activator of Formula II,

and renal carcinoma as the solid tumor, which were elected in the reply filed on February 19, 2008.

Priority

The present application is a 371 of PCT/IB03/06375 filed on 10/02/2003, and claims priority to EPO 02292963.2 filed on 12/02/2002.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103 (New Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 80-88, 90-95 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over BioNews (http://www.investinbiotech.com/pressroom_release.php?id+644, July 8, 2002, cited in

prior office action) in view of Espinosa et. al. (Journal of Biological Chemistry (2001) 276:18337-18344, cited in prior office action).

Claims 80-81, 88, 90-93 and 102 recite a method of treating renal carcinoma (species elected for solid tumor) comprising the administration of Phosphostim (BrHPP) (species elected for gamma-delta T activator) and a pharmaceutically acceptable carrier in an amount sufficient to induce an increase in the gamma-delta T cell population (5-fold increase in claim 80, 10-fold in claim 81) in a subject having renal carcinoma.

Claim 86, further limits claim 80, wherein said gamma-delta T cell activator is provided in an amount sufficient to expand the gamma-delta T cell population in a subject to reach between 30-90% of total circulating lymphocytes in a subject.

Claim 87, further limits claim 80, wherein the biological activity of gamma-delta T cells is increased in said subject.

For claims 80-81, 86-88, 90-93 and 102, BioNews teaches a method of treating renal carcinoma with Phosphostim, an activator of T gamma-delta cells..

BioNews does not teach the use of a pharmaceutical acceptable carrier and the amounts of Phosphostim to be administered to the patient in order to induce an increase in the gamma-delta T cell population in the subject having renal carcinoma. However, Espinosa teaches a composition comprising BrHPP (Phosphostim) in water (i.e. a pharmaceutically acceptable carrier, see page 18338, last three lines of the first paragraph of left column). Espinosa further teaches that a solution of BrHPP increases the gamma-delta T cell population among total T cells in culture up to 20% at 12.5

nanomolar, 30% at 25 nanomolar and 50% at 100 nanomolar (see page 18340, Figure 4 B).

The statement in claim 90: "wherein Phosphostim (gamma-delta T cell activator elected) is capable of inducing the proliferation of a gamma-delta T cell in a pure population of gamma-delta T cell clones when said compound is present in culture at a concentration of less than 1 mM" is an inherent property of Phosphostim since the same compound should always have the same properties. MPEP 2112 I states: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." Since the prior art already discloses the compound Phosphostim, and since the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior

art does not possess the same material, structural and functional characteristics of the claimed product, in the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from the product taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to treat patients with renal carcinoma comprising the administration of Phosphostim (BrHPP) as taught by BioNews, and further comprising a pharmaceutically acceptable carrier as taught by Espinosa, with the motivation of better delivering the active ingredient Phosphostim (BrHPP) to the patient. It would be further obvious to adjust the amount of Phosphostim (BrHPP) to be administered to the patient in order to increase the activity of gamma-delta T cells *in vivo*, based in the amounts disclosed by Espinosa *in vitro*, since the skilled in the art will be able to extrapolate *in vitro* data into *in vivo* data and further determine the specific amount of Phosphostim to be administered to a particular patient and adjust the dosage amounts based on the observed clinical effectiveness and the amount of increase in the gamma-delta T cell population , thus resulting in the practice of claims 80-81, 86-88, 90-93 and 102 with a reasonable expectation of success.

Claim 82 further limits claim 80, wherein at least two treatments are administered to subject.

Claim 83, further limits claim 80, wherein at least four treatments are administered to subject.

Claim 84, further limits claim 80, wherein Phosphostim is administered in more than one treatment with an interval of about two to about eight weeks between treatments.

Claim 85, further limits claim 80, wherein Phosphostim is administered in more than one treatment with an interval of about three to about four weeks between treatments.

Claim 94 further limits claim 92, wherein Phosphostim is administered in a dose to humans between 10 mg/kg to 100 mg/kg.

Claim 95 further limits claim 92, wherein Phosphostim is administered by intravenous infusion in a dose to humans that is calculated according to formula I.

For claims 82-85 and 94-95, Espinosa further teaches that a solution of BrHPP increases the gamma-delta T cell population among total T cells in culture up to 20% at 12.5 nanomolar, 30% at 25 nanomolar and 50% at 100 nanomolar (see page 18340, Figure 4 B).

BionNews in view of Espinosa teach all the limitations of claims 82-85 and 94-95, except for the dose frequency of administration and the exact dosage. However, it's within the capability of the ordinary artisan to adjust the frequency of administration and dosage amounts based on the observed clinical effectiveness, thus resulting in the practice of claims 82-85 and 94-95 with a reasonable expectation of success.

Claims 100-101 and 104-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over BioNews (http://www.investinbiotech.com/pressroom_release.php?id+644, July 8, 2002, cited in prior office action) as evidenced by Espinosa et. al. (Journal of Biological Chemistry (2001) 276:18337-18344, cited in prior office action) as applied to claims 80-88, 90-95 and 102 above, and further in view of Negrier et. al. (The New England Journal of Medicine, (1998) 338:1272-1278, cited in prior office action).

Claim 100 further limits claim 80, further comprising separately administering to a subject in need thereof an effective amount of Phosphostim and an interleukin-2 (IL-2) polypeptide.

BioNews in view of Espinosa teach all the limitations of claim 100, except for the administration of an interleukin-2 polypeptide. However, Negrier et. al. teach that Interleukin-2 induces notable tumor regression in a limited number of patients with metastatic renal-cell carcinoma (see title and abstract).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat renal cancer combining two compositions (Phosphostim and Interleukin-2) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205

USPQ 1069, 1072 (CCPA 1980). Thus resulting in the practice of claim 100, with a reasonable expectation of success.

Claim 101 further limits claim 100, wherein the IL-2 polypeptide is administered over a period of time between 1 and 10 days.

Claim 104, further limits claim 100, wherein the IL-2 is administered subcutaneously and BrHPP (Phosphostim) is administered intravenously.

Claim 105, further limits claim 104, wherein IL-2 is administered at a daily dose of between 0.2 and 2 MU per day.

Claim 106 further limits claim 104, wherein said IL-2 is administered at a daily dose between 0.2 and 1.5 MU per day.

Claim 107 further limits claim 104, wherein IL-2 is administered at a daily dose of between 0.2 and 1 MU per day.

For claim claims 101 and 104-107, Negrier further teaches that interleukin-2 was administered as a five-day continuous intravenous infusion at a dose of 18×10^6 IU per square meter of body surface area per day (see page 1273, under treatment, second paragraph).

Negrier does not teach the exact amounts and dose regimen disclosed in claims 101 and 104-107. However, it's within the capability of the ordinary artisan to adjust the dose regimen based on the observed clinical effectiveness, thus resulting in the practice of claims 101 and 104-107 with a reasonable expectation of success.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 103 (a)

Upon careful consideration the 103(a) rejection is withdrawn.

However, based on new considerations a new 103(a) rejection is applied (see above).

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
August 19, 2009

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612